II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 52-82 were pending in the case at the time of the Action. Claims 52 and 79 have been amended in the Amendment set forth herein. Support for the Amendment can be found generally throughout the specification, such as in FIG. 1-3, 7, 8, 16, 21, 49, 59, each of which depict the chemical structure of ethylenedicysteine (EC) (a dicarboxylic acid) and certain EC-targeting ligand conjugates. No claims have been added, and no claims have been canceled. Thus, claims 52-82 are pending in the case.

B. The Rejections Under 35 U.S.C. §102 are Overcome

1. Rejection Based on Anderson *et al.*

Claims 52, 54, 55, 63, and 65 have been rejected under 35 U.S.C. §102(b) as being anticipated by Anderson *et al.* Anderson *et al.* is said to disclose N,N'-ethylene-di-L-cysteine (EC) complexes of Ga (III) and In(III) that contain two nitrogens and two sulfurs (N2S2) that are said to be possible myocardial PET imaging agents. Applicants respectfully traverse.

The claims at issue pertain to methods of imaging that involve administering to the subject an effective amount of a composition comprising a radionuclide-labeled bis-aminoethanethiol (BAT) dicarboxylic acid-targeting ligand conjugate

It is first respectfully submitted that the Anderson *et al.* article only makes reference to the observation that an indium complex with excellent *in vivo* stability "is desirable when designing bifunctional chelates to be conjugated to larger molecules such as antibodies or peptides." (page 165, col. 1) However, this statement does not identify any BAT conjugate *per se*, and, more importantly, the article itself suggests that it would be unpredictable whether a chelate conjugated to a protein or peptide would be stable *in vivo* ("the nature of the bifunctional

chelate use to complex radiometals to proteins or peptides also alters the uptake and in clearance organs..." page 165, sentence bridging columns 1 and 2).

In the Conclusion section, the article states that "[i]t would be interesting to compare the biodistribution" of an indium labeled EC analogue conjugated to a "protein or peptide" or other indium labeled conjugates. (page 172, col. 2) However, the article further teaches the uncertainty of whether such conjugates would prove to have sufficient stability, noting that "[t]he accumulation of radiolabeled ligand complexes in the liver without clearance may be indicative of complex instability" and that "[t]his needs to be further investigated" (page 172, col. 1).

From the foregoing passages, it appears that the authors simply do not have any degree of certainty whether EC conjugates would be sufficiently stable to be useful. They merely state, in effect, that it would be "interesting" to find out the answer to this question. Accordingly, Anderson *et al.* is nothing more than an "obvious to try" reference. This type of rejection is improper as a matter of law. Applicants turn to *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988), which held that, in order for a reference or references to obviate an invention, it must be shown that the reference (or references) contains:

(1) detailed enabling methodology for practicing the claimed invention;

(2) a suggestion for modifying the prior art to practice the claimed invention; and

(3) evidence suggesting that the invention would be successful.

It is submitted that the present references relied upon by the Examiner clearly fail to satisfy this tripartite test of *O'Farrell*. In particular, for the reasons discussed above, Anderson *et al.* does not provide any reasonable expectation that such a combination would be successful and they fail to provide detailed enabling methodology for practicing the claimed invention, *e.g.*, for constructing the claimed conjugate. Moreover, there is no evidence that such a conjugate, once constructed, would actually function appropriately as an imaging agent.

In *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991), the Federal Circuit took the *O'Farrell* doctrine a step further. In *Vaeck* the Federal Circuit stated that in order for an Examiner to make out a *prima facie* case of obviousness two things must be shown:

(1) that the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition; and

(2) that the prior art must demonstrate a reasonable expectation of success of the invention.

The court went on to emphasize that both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the Applicant's disclosure. Here, for the reasons discussed above, we have neither.

Regarding dependent claim 55, the Examiner has not set forth any disclosure in Anderson *et al.* pertaining to any tissue-specific targeting ligand. As to dependent claim 65, the Examiner has not identified any disclosure in Anderson *et al.* pertaining to a radionuclide-labeled ethylenedicysteine-targeting ligand conjugate. For the reasons set forth above, Applicants find no such disclosure in Anderson *et al.*, nor is there any disclosure that a conjugate, once constructed, would actually function appropriately as an imaging agent.

For each of the reasons set forth above, Anderson *et al.* fails to anticipate claims 52, 54, 55, 63, and 65. Therefore, it is respectfully requested that this rejection should be withdrawn.

2. Rejection Based on Kung *et al.*

Claims 52, 54-56, 58, and 63 have been rejected under 35 U.S.C. §102(b) as being anticipated by Kung *et al.* Kung *et al.* is said to disclose bisaminoethanethiol (BAT) derivatives that are possible ligands for 99mTc brain imaging agents. Applicants respectfully traverse.

Without conceding that the claims as originally written were anticipated by Kung *et al.*, Applicants point out the claim 52 (and its dependent claims) now recites the limitation

"administering to the subject an effective amount of a composition comprising a radionuclide-labeled bis-aminoethanethiol (BAT) ***dicarboxylic acid*** -targeting ligand conjugate." (emphasis added).

Applicants have reviewed the sections of Kung *et al.* cited by the Examiner. It appears to Applicants that none of these sections expressly or necessarily disclose any targeting ligand, or any targeting ligand conjugated to a bis-aminoethanethiol (BAT). Nor do the sections of Kung *et al.* cited by the Examiner that allegedly pertain to imaging disclose any method of imaging that involve use of a bis-aminoethanethiol (BAT) dicarboxylic acid -targeting ligand conjugate, or any suggestion that a bis-aminoethanethiol (BAT) dicarboxylic acid -targeting ligand conjugate, once constructed, would appropriately function as an imaging agent.

Regarding dependent claim 55, the Examiner has not set forth any disclosure in Kung *et al.* that expressly or necessarily discloses any targeting ligand that is a tissue-specific ligand, nor has the Examiner identified any disclosure that indicates that any such construct, once constructed, would function as an imaging agent.

In view of the above, Kung *et al.* fails to anticipate claim 52, 54-56, 58, and 63. Therefore, it is respectfully requested that this rejection should be withdrawn.

3. Rejection Based on McBride *et al.*

Claims 52, 55, 56, 57, 58, 61, 62, 63, 66, and 79 have been rejected under 35 U.S.C. §102(b) as being anticipated by McBride *et al.* McBride *et al.* is said to disclose radioactive peptides that may be used as therapeutic or diagnostic agents for analyzing a mammalian body, and that small linear synthetic peptides that are somatostatin analogs which incorporate BAT chelators may be labeled with Tc-99m. Applicants traverse.

As set forth above, claim 52 (and its dependent claims) now recites the limitation "administering to the subject an effective amount of a composition comprising a radionuclide-

labeled bis-aminoethanethiol (BAT) ***dicarboxylic acid*** -targeting ligand conjugate." (emphasis added). Applicants have reviewed the sections of McBride *et al.* cited by the Examiner, and it appears to Applicants that the conjugates set forth in McBride *et al.* are distinct from the conjugates of the claimed invention because the conjugates set forth in McBride *et al.* do not include an ethane backbone. The Examiner has cited column 13, lines 18-21, which recite "[t]he invention also provides small linear synthetic peptides that are somatostatin analogues and incorporate bisamine bisthiol (BAT) chelators that may be labeled with Tc-99m." Applicants point out that there is no indication in this section that the chelators are "bis-aminoethanethiol (BAT) dicarboxylic acid -targeting ligand conjugate." In particular, there is no indication that the "bisamine bisthiol" chelators set forth in McBride *et al.* are bisaminoethanethiol chelators (more particularly, chelators with an ethane backbone). Nor is there any disclosure setting forth that the chelators referred to in McBride *et al.* are dicarboxylic acids.

Regarding dependent claim 57, the Examiner has additionally not set forth any disclosure in McBride *et al.* pertaining to imaging using any bis-aminoethanethiol (BAT) dicarboxylic acid -targeting ligand conjugate in a human. Regarding dependent claim 66, the Examiner has not identified any disclosure in McBride *et al.* pertaining to a targeting ligand that is an anticancer agent, a DNA topoisomerase inhibitor, or any of the other classes of targeting ligands set forth in claim 66. Regarding claim 79, the Examiner has not identified any disclosure pertaining to a linker conjugated that BAT dicarboxylic acid to a targeting ligand, nor is there any suggestion that such a conjugate, if available, would function as an imaging agent.

In view of the above, it is respectfully submitted that the rejection of claims 52, 55, 56, 57, 58, 61, 62, 63, 66, and 79 under 35 U.S.C. §102(b) should be withdrawn.

C. The Rejections Under 35 U.S.C. §102 are Overcome

1. Rejections Based on Anderson *et al.*

Claims 52, 57, and 64 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Anderson *et al.* Anderson *et al.* is said to fail to specifically disclose a method of imaging wherein 68Ga is utilized. The Examiner argues that it would have been obvious to one of ordinary skill in the art to use a 68Ga labeled targeting agent because Anderson discloses that 68Ga-EC has potential as a possible PET imaging agent. Anderson *et al.* fails to disclose administration to humans, and this is said to be obvious since rats and humans are mammals. Applicants respectfully traverse.

In rejecting claims under 35 U.S.C. §103, the Examiner bears the initial burden of presenting a *prima facie* case of obviousness. See *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). In order to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) the prior art reference (or references when combined) must teach or suggest all the claim limitations; (2) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (3) there must be a reasonable expectation of success. *Manual of Patent Examining Procedure* § 2142. See also *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed Cir. 1991) (emphasizing that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must be both found in the prior art, and not based on applicant's disclosure). It is important to note that all three elements must be shown to establish a *prima facie* case of obviousness. Thus, if one element is missing, a *prima facie* case of obviousness does not exist.

In accordance with *In re Vaeck*, the Examiner has failed to establish a *prima facie* case of obviousness as to claim 52 and each of its dependent claims because she has not set forth that

Anderson *et al.* teaches or suggests each limitation of the claimed invention. Claim 52 pertains to a method of imaging a site within a subject that involves administering to the subject an effective amount of a composition that includes a radionuclide-labeled bis-aminoethanethiol (BAT) dicarboxylic acid-targeting ligand conjugate, and detecting a radioactive signal from the site by emission tomography. The discussion above pertaining to the disclosure in Anderson *et al.* is herein incorporated into this section. More particularly, the Examiner has not cited any teaching or suggestion in Anderson *et al.* to provide for a radionuclide-labeled bis-aminoethanethiol (BAT) dicarboxylic acid-targeting ligand conjugate. Nor do the Applicants identify any such teaching or suggestion. Applicants invite the Examiner to specifically point out any teaching or suggestion pertaining to a radionuclide-labeled bis-aminoethanethiol (BAT) dicarboxylic acid-targeting ligand conjugate, and any teaching or suggestion indicating that such a conjugate, if available, would function as an imaging agent.

Regarding dependent claim 57, the Examiner has not identified any teaching or suggestion pertaining to methods of imaging that involve administration of a radionuclide-labeled bisi-aminoethanethiol (BAT) dicarboxylic acid conjugate to a human subject. It appears to Applicants that Anderson *et al.* contemplates rats as subjects, and not humans. Applicants invite the Examiner to point out any teaching or suggestion pertaining to human subjects.

For the reasons set forth above, Anderson *et al.* fails to render obvious the invention set forth in claims 52, 57, and 64. Therefore, it is respectfully requested that the rejection of these claims based on Anderson *et al.* under 35 U.S.C. §103(a) should be withdrawn.

2. Rejections Based on Kung *et al.*

Claims 52 and 57 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Kung *et al.* Kung *et al.* is discussed above. Kung is said to fail to disclose administration of a BAT conjugate to a human. The Examiner asserts that it would be obvious to administer the

radiolabeled BAT conjugate to a human because both the rat and human are mammals. Applicants traverse.

In accordance with *In re Vaeck*, Kung *et al.* fails to render obvious the claimed invention because it does not teach or suggest each limitation of the claimed invention. The discussion above pertaining to the disclosure in Kung *et al.* is herein incorporated into this section. In particular, the Examiner has not identified any teaching or suggestion in Kung *et al.* to provide for any radionucleide-labeled bis-aminoethanethiol (BAT) dicarboxylic acid-targeting ligand conjugate. It appears to Applicants that none of the sections of Kung *et al.* cited by the Examiner teach or suggest any targeting ligand, or any targeting ligand conjugated to a bis-aminoethanethiol (BAT). Nor do the sections of Kung *et al.* cited by the Examiner that allegedly pertain to imaging teach or suggest any method of imaging that involves use of a bis-aminoethanethiol (BAT) dicarboxylic acid -targeting ligand conjugate, or any suggestion that a bis-aminoethanethiol (BAT) dicarboxylic acid-targeting ligand conjugate, once constructed, would appropriately function as an imaging agent.

Therefore, because the Examiner has failed to meet her burden of showing that Kung *et al.* teaches or suggests each limitation of the claimed invention, there can be no *prima facie* case of obviousness. Therefore, it is respectfully requested that the rejection of claims 52 and 57 should be withdrawn.

3. Rejections Based on Auzeloux *et al.*

Claims 52, 54-56, 58, 62-63, 66, 69, and 79 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Auzeloux *et al.* Auzeloux *et al.* is said to disclose Tc-99m bisaminoethanethiol (BAT) derivatives that have potential as a melanoma tracer agent. Applicants respectfully traverse.

There is no *prima facie* case of obviousness because the Examiner has not met her burden of showing that Auzeloux *et al.* teaches or suggests any targeting ligand conjugated to a bisaminoethanethiol (BAT) dicarboxylic acid chelator.

Applicants have reviewed the sections of Auzeloux *et al.* cited by the Examiner, and Applicants identify no teaching or suggestion in any of these sections pertaining to a dicarboxylic acid. Nor do Applicants identify any such disclosure in other sections of Auzeloux *et al.* Applicants invite the Examiner to identify any such teaching or disclosure.

Further, the Examiner has not identified any teaching or suggestion in Auzeloux *et al.* pertaining to any agent that is conjugated to a targeting ligand. Applicants have reviewed the sections of Auzeloux *et al.* cited by the Examiner, and find no teaching or suggestion pertaining to targeting ligands in these sections. Applicants invite the Examiner to point out any such teaching or suggestion.

Furthermore, the Examiner cited any teaching or suggestion that any such conjugates, once available, would successfully function as an imaging agent. Nor has the Examiner cited any disclosure in Auzeloux *et al.* that teachings or suggests administration of any bisaminoethanethiol (BAT) dicarboxylic acid targeting ligand conjugate to a human.

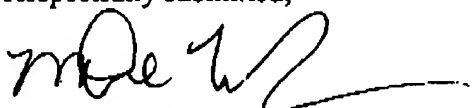
Regarding dependent claim 55, the Examiner has not identified any teaching or suggestion in Auzeloux *et al.* pertaining to any targeting ligand that is a tissue-specific ligand. Regarding dependent claim 66, the Examiner has not identified any teaching or suggestion in Auzeloux *et al.* pertaining to any of the classes of targeting ligands set forth in this claim. Regarding claim 69, the Examiner has not identified any teaching or suggestion in Auzeloux *et al.* pertaining to any targeting ligand that is a tumor marker. Nor has the Examiner cited any teaching or suggestion in Auzeloux *et al.* pertaining to a targeting ligand that includes a linker conjugating the BAT dicarboxylic acid to the targeting ligand (claim 79).

In view of the above, the Examiner has failed to set forth that Auzeloux *et al.* teaches or suggests each limitation of the claimed invention, and thus there can be no *prima facie* case of obviousness. Therefore, it is respectfully requested that the rejection of claims 52, 54-56, 58, 62-63, 66, 69, and 79 should be withdrawn.

D. Conclusion

Applicants believe that the present document is a full and complete response to the Office Action dated November 4, 2005. Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance. Should the Examiner have any question, please contact the undersigned below at 512-536-5639.

Respectfully submitted,



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